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Absence of Pubertal Gonadotropin Secretion in Girls with McCune-Albright Syndrome

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ABSTRACT. Precocious puberty in girls with McCune-Albright syndrome has been attributed in some cases to early activation of the hypothalamic-pituitary-gonadal axis and in other cases to sex steroid secretion by apparently autonomous ovarian cysts. We evaluated serum gonadotropins and sex steroids in six girls (aged 1–9 yr) with McCune-Albright syndrome. The children had Tanner stage II–IV pubertal development. In five patients, nocturnal gonadotropin concentrations and the gonadotropin response to LHRH were within the normal range for prepubertal children. Thus, the precocious puberty in these patients could not be explained by activation of the hypothalamic-pituitary-ovarian axis. One child had high amplitude nocturnal pulses of serum LH and a LH-predominant response to LHRH. She was the oldest of the six girls and had a bone age of 13.5 yr which is within the range in which hypothalamic-pituitary-ovarian activation normally occurs. The children all had ovarian enlargement and ovarian cysts determined by ultrasound. It appears that precocious puberty in McCune-Albright syndrome may result from ovarian estrogen secretion in the absence of normal pubertal activation of the hypothalamic-pituitary-ovarian axis. (*J Clin Endocrinol Metab* **58:** 1161, 1984)

PATIENTS with the classic form of McCune-Albright syndrome have a triad of precocious puberty, fibrous dysplasia of bone, and *café au lait* skin pigmentation (1). The mechanism of precocious puberty in McCune-Albright syndrome is controversial. Several researchers postulated that there is early activation of the hypothalamic-pituitary-gonadal axis (true precocious puberty) (2–6). Others presented evidence that the ovaries may produce sex steroids autonomously resulting in premature development of secondary sexual characteristics (precocious pseudopuberty) (6–11). We evaluated serum gonadotropin and estrogen levels in six girls with McCune-Albright syndrome. The underlying mechanism of precocious puberty in five of the six girls appeared to be ovarian estrogen secretion independent of pubertal hypothalamic-pituitary activation.

Materials and Methods

Subjects (Tables 1 and 2)

Patients 1, 2, and 3 had classic McCune-Albright syndrome, with precocious puberty, *café au lait* skin pigmentation, and radiographic evidence of fibrous dysplasia of bone. Patients 4, 5, and 6 had precocious puberty and radiographic evidence of fibrous dysplasia of bone without pigmented skin lesions. The diagnosis of fibrous dysplasia of bone was confirmed by biopsy in patient 6. Coexistence of fibrous dysplasia of bone and precocious puberty in the absence of abnormal skin pigmentation has been recognized as a variant form of McCune-Albright syndrome (8). Patients were included in the study only after exclusion of brain, adrenal, or ovarian neoplasms by computed tomography of the head and ultrasonography of the adrenal and pelvic regions. Plasma 17-hydroxyprogesterone and 11-deoxycortisol levels, which were measured to exclude congenital adrenal hyperplasia, were normal in all patients. Serum T_4, free T_4, and TSH levels were normal.

We studied five normal girls, who were below 10 yr of age and had Tanner stage I breast and pubic hair development, to determine normal nocturnal gonadotropin levels and responses to LHRH in prepubertal girls. We also obtained pubertal data from five 10- to 15-yr-old normal girls, who had Tanner stage II–IV breast and pubic hair development.

Protocol

Patients were admitted to the Clinical Center of the NIH. The protocol was approved by the Clinical Research Committee of the NICHD. We obtained informed consent from either parent and assent from the children above age 7 yr. We measured serum gonadotropin levels every 20 min from 1000–1400

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TABLE 1. Clinical features of six girls with McCune-Albright syndrome

Patient no.	Age (yr)	Age of onset (yr)[a]	Ht		Stages of puberty[b]		Menses	*Café au lait* pigmentation
			cm	Percentile	Breast	Pubic Hair		
1	4.5	1.3	107	60	III	IV	+	+
2	5.1	3.5	128	>97	IV	III	+	+
3	5.2	0.6	102	25	II	II	+	+
4	1.2	0.7	82	95	IV	II	+	—
5	4.5	2.5	117	>97	IV	II	+	—
6	8.9	5.5	152	>97	IV	III	+	—

+, Present; —, absent.

[a] Onset of secondary sexual characteristics or vaginal bleeding.

[b] According to the classification of Tanner (24).

TABLE 2. Radiographic and cytological data in six girls with McCune-Albright syndrome

Patient no.	Age (yr)	Bone age (yr)	Bone lesions	Vaginal maturation index score[a]	Ovarian vol (cm^3)[b]		Ovarian cysts	
					Right	Left	Right	Left
1	4.5	7.8	+	46	1.4	2.7	Sm	Sm
2	5.1	8.8	+	53	0.6	9.6	Sm	Lg (2 cm)
3	5.2	6	+	48	A	1.7	Sm	Sm
4	1.2	2	+	50	1.0	13	Sm	Lg (2–3 cm)
5	4.5	6.8	+	41	2.6	1.9	Sm	Sm
6	8.9	13.5	+	52	13.1	4.0	Sm	Sm

+, Present; A, Absent; Sm, small (<8 mm); Lg, large (>8 mm).

[a] Score = % superficial cells ± 0.5 (% intermediate cells) on vaginal cytological examination (25).

[b] 0.5 × (sagital diameter) × (anterior-posterior diameter) × (transverse diameter), measured by ultrasound (18).

h (daytime levels) and from 2200–0200 h (nighttime levels). In patients 4 and 5, serum gonadotropin levels were determined from 1100–1400 h and from 2300–0200 h. We measured plasma estradiol and estrone levels four times (at the beginning and end of each period of sampling for gonadotropins). Serum LH bioactivity was determined hourly from 2300–0200 h. On the morning of day 2, we performed a LHRH stimulation test. We injected 100 μg LHRH, iv at time zero and measured serum gonadotropin levels at -30, -15, 0, 15, 30, 45, 60, 90, 120, and 180 min in the patients and pubertal controls and at 0, 15, 30, 45, and 90 min in the prepubertal controls.

Hormone assays

LH, FSH, estradiol, and estrone were measured by modifications of previously described methods (12–14). The sensitivity limits for these assays were 0.3 mIU/ml (Second International Reference Preparation of human menopausal gonadotropin), 0.2 mIU/ml, 20 pg/ml, and 12–20 pg/ml, respectively. Intraassay and interassay coefficients of variation were respectively, 9% and 16% for estrone, 8% and 16% for estradiol, 7% and 12% for LH, and 5% and 14% for FSH. LH was also measured in the patients by a previously described rat Leydig cell bioassay (15). LER-907 was used as the reference preparation for this assay to permit comparison with published values for LH bioactivity in normal prepubertal and pubertal subjects. All samples were measured in one assay, and the intraassay coefficient of variation was 5%. Unless stated otherwise the mean ± 1 SEM are given.

Statistical analysis

Statistical analysis was performed using Student's *t* test.

Results

Nocturnal gonadotropin secretion (Fig. 1A and Table 3)

Patients 1 through 5 had nocturnal LH and FSH secretion within the range for normal prepubertal children. The gonadotropin levels in patient 6 exceeded those for prepubertal children and were within the range for normal pubertal children.

Gonadotropin response to LHRH (Fig. 1B and Table 3)

Patients 1 through 5 showed minimal elevation of LH in response to LHRH, within the range seen for normal prepubertal children. Patient 6 had a marked elevation of LH in response to LHRH, similar to the rise in normal pubertal subjects.

Bioactive LH concentrations (Table 4)

To assess the possibility that patients 1 through 5 might have LH bioactivity that did not cross-react in the LH RIA, we measured LH concentrations using a rat Leydig cell bioassay. Nighttime bioactive LH concentrations in patients 1 through 5 did not exceed the levels reported in normal prepubertal children. Bioactive LH in patient 6 was within the range in normal pubertal subjects.

Plasma estrogen concentrations and ovarian volume by ultrasound (Tables 2 and 4)

The five patients with a prepubertal pattern of gonadotropin secretion had estradiol levels that ranged from below the assay detection limit to 133 pg/ml (Table 4). Mean ovarian volumes were increased compared to prepubertal levels [0.9 ml (18)] in every case (Table 2). Patient 4, who had the highest estradiol level, also had a large left ovarian cyst. Patient 3 previously had excision of the right ovary because of a large cyst.

Discussion

All patients in this study had McCune-Albright syndrome with premature pubertal development and menses. The underlying mechanism of the precocious puberty in patients 1 through 5 appeared to be independent of

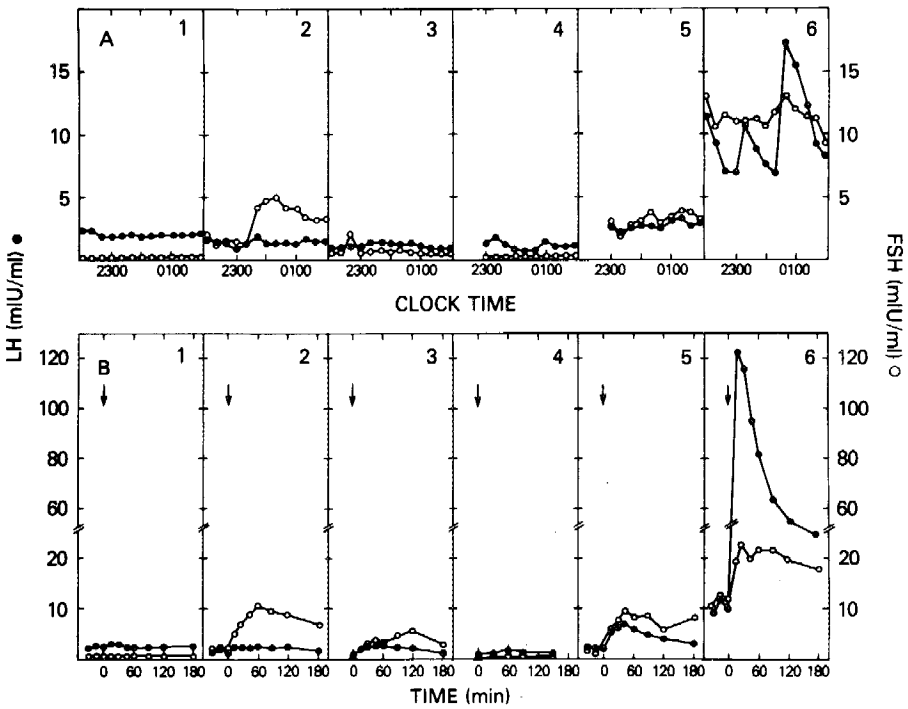

FIG. 1. Serum gonadotropin levels in girls with McCune-Albright syndrome. A, Nocturnal serum gonadotropin levels, measured every 20 min during the time period indicated. B, Serum gonadotropin levels before and after a 100 μg iv bolus of LHRH given at time zero, as indicated by the *arrow*.

TABLE 3. Clinical features and gonadotropin concentrations of normal prepubertal and pubertal subjects

Pubertal stage[a]	Age (yr)	Nocturnal gonadotropin conc. (mIU/ml)		LHRH-stimulated gonadotropin concentrations (mIU/ml)[b]			
				LH		FSH	
		LH	FSH	Basal	Peak	Basal	Peak
Prepubertal							
I (5)[c]	6.7 ± 2.2	5.9 ± 0.4	7.7 ± 1.1	5.4 ± 4.0	12.3 ± 4.5	7.8 ± 6.0	39.0 ± 15.4
Pubertal							
II (1)	10.9	17.1	10.4	12.8	28.9	12.5	20.6
III (3)	11.7 ± 0.9	10.8 ± 4.7	9.0 ± 3.1	6.6 ± 4.2	55.4 ± 42.3	8.1 ± 3.6	17.1 ± 1.8
IV (1)	13.8	4.3	4.6	4.4	204	3.0	11.3
Mean (5)	12.2 ± 1.3	10.8 ± 5.1	8.5 ± 2.7	7.4 ± 3.8	79.8 ± 73.8	8.0 ± 4.0	16.6 ± 3.6

Data in this table are the mean ± 1 SD.
[a] According to the classification of Tanner (24).
[b] See *Materials and Methods* for sampling protocols.
[c] The number of subjects is in parentheses.

pubertal activation of the hypothalamic-pituitary axis. These patients had nocturnal and LHRH-stimulated gonadotropin concentrations that did not differ from those in normal prepubertal subjects. Patient 6 had large nocturnal LH pulses, similar to those in normal pubertal subjects, and a pubertal gonadotropin response to LHRH. Since she was the oldest patient in the series and had a bone age within the range in which pubertal activation of gonadotropin secretion normally occurs (19), it cannot be presumed that her gonadotropin levels were elevated when precocious puberty first began.

Several previously reported patients with McCune-Albright syndrome were thought to have true precocious puberty as the mechanism for early sexual development. Benedict (9) described two girls, both age 9 yr, with elevated urinary FSH levels determined by bioassay. Husband and Snodgrass (3) described another 9-yr-old girl with elevated urinary FSH levels. Lightner *et al.* (4) described a 6-yr-old boy with elevated serum LH and FSH levels. A 6-yr-old boy with McCune-Albright syndrome and spermatogenesis on testicular biopsy also was reported previously (2). Gonadotropin data were not available in this boy. Based upon these reports, Hall and Warnick (5) postulated a hypothalamic mechanism of

TABLE 4. Plasma estrogen, determined by RIA, and serum LH concentrations, determined by bioassay

Patient no.	Plasma estrogen conc. (pg/ml)		Bioactive LH conc. (ng/ml)[a]
	Estradiol	Estrone	
1	21 ± 2	24 ± 6	<31
2	31 ± 5	<20	ND[b]
3	<20	<20	<31
4	133 ± 22	18 ± 3	<31
5	<20	<20	32 ± 1
6	50 ± 4	63 ± 10	>500
Normal values			
Prepubertal	<20	<20	12.4 ± 5.4 (5.9–23.7)[c]
Late pubertal	60 ± 30 (<20–209)[d]	58 ± 22 (24–163)[d]	270 ± 287 (40–720)[c]
Adult early follicular[e]	<10–100	30–110	
Adult midcycle[e]	170–770		
Adult midluteal[e]	190–340	85–180	

[a] Reference standard LER-907.

[b] Not done.

[c] From Lucky *et al.* (16, 17). Late pubertal subjects were postmenarcheal and age 16 yr or younger. The values are the mean ± 1 SD, with the range in parentheses.

[d] Six girls (13–15 yr) with Tanner pubertal stages III–V. Values were determined as described in *Materials and Methods*, and are the mean ± 1 SEM, with the range in parentheses.

[e] Normal adult ranges for our laboratory.

precocious puberty in McCune-Albright syndrome.

A pseudopuberty mechanism has also been proposed. Pray (10) observed regression of secondary sexual characteristics and a decrease in serum estrogens after excision of an ovarian cyst in a 4-yr-old girl. Similar regression of sexual characteristics after excision of ovarian cysts was reported in other girls (6, 9). D'Armiento *et al.* (7) and Danon *et al.* (6) found low gonadotropin levels in a 5-yr-old girl and a 6-month-old girl with McCune-Albright syndrome.

These previous reports of functioning ovarian cysts in patients with McCune-Albright syndrome are consistent with our observations. Patient 4 had the highest initial level of estradiol and also had a large left ovarian cyst. Patient 5 had a history of cyclical appearance and disappearance of secondary sexual characteristics before her referral. After her initial studies, patient 2 had marked fluctuations in plasma estradiol levels that correlated with the size of her left ovarian cyst (20). Patients 1, 2, 3, and 5 had low to undetectable estradiol levels when studied, but had breast development and a history of vaginal bleeding, which provided clinical evidence of previously elevated estrogen secretion. This is a further indication that episodic estradiol secretion occurs in girls with McCune-Albright syndrome and may indicate that intermittently functioning ovarian cysts were present in all five girls with low gonadotropin levels.

Although there may be two different mechanisms of precocious puberty in McCune-Albright syndrome, it would be more satisfying to reconcile the seeming true puberty and pseudopuberty with one underlying process. The three girls previously reported with evidence of true puberty were all initially studied at 8 yr of age or older, as was patient 6 in the current study. Thus, it is conceivable that these children first had pseudopuberty independent of pubertal activation of the hypothalamic-pituitary unit. The elevated sex steroid levels may have subsequently caused early maturation of the hypothalamic-pituitary axis and the onset of true precocious puberty. A similar mechanism was postulated in children with congenital adrenal hyperplasia, who may develop true precocious puberty complicating their underlying pseudopuberty (21–23). Regardless of whether there are one or two mechanisms of precocious puberty in McCune-Albright syndrome, our observations suggest that a pseudopubertal mechanism usually underlies premature sexual development in young girls with this disorder. True puberty appears to be uncommon.

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